Title of the PhD project: Structure and interactions of the propeptide of lysyl oxidase

Disciplines: Biochemistry - Structural Biology
Laboratory: (ICBMS, UMR 5246, Dir: Olivier Piva, team Extracellular and Pericellular Supramolecular Assemblies, Head: Sylvie Ricard-Blum)
Doctoral school: Interdisciplinary Doctoral program in health-sciences (EDISS) - ED 205

Description
Scientific background and rationale: Lysyl oxidase is an amine oxidase, which is secreted as a proenzyme and catalyzes the first step of collagen and elastin cross-linking in the extracellular matrix (ECM). Its proteolytic activation releases the N-terminal propeptide, which is involved in ECM assembly, acts as a tumor suppressor, inhibits cell signaling, and stimulates adipogenesis. The propeptide is intrinsically disordered and may fold upon binding to its partners. Preliminary interaction data have been obtained by the team for the propeptide.

Aim: The aims of the project is i) to identify extracellular and membrane partners of the propeptide in order to determine if it has further functions, ii) to study if and how it interferes with ECM enzymatic cross-linking, iii) to characterize the 3D structure of the complexes formed by the propeptide and its partners, and iv) to determine the impact of the R158Q mutation, which inhibits the pro-adipogenic and anti-tumoral activities of the propeptide, on the above processes.

Description of the project methodology: The propeptide and its potential partners will be expressed under a recombinant form in prokaryotic and eukaryotic cells. The interactions of the purified proteins will be identified and characterized (kinetics and affinity) by Bio-Layer Interferometry. Binding sites will be localized in vitro and/or in silico by molecular modeling. The structure of supramolecular complexes will be studied by small-angle X-ray scattering, small-angle neutron scattering and cryo-electron microscopy.

Expected results and perspectives: This project will allow to determine if the propeptide interacts via different molecular recognition processes to its different partners and to decipher the molecular mechanism(s) underlying its role in ECM assembly and cross-linking, adipogenesis and cell signaling. It will also give molecular insights on the effect of the R198Q mutation, which is associated with an increased risk of breast cancer.

Skills required: The applicants should have backgrounds in protein biochemistry, molecular biology, biophysics and structural biology.

Bibliography:

Keywords: Extracellular matrix, Bioactive fragments, Intrinsic disorder, Biomolecular interactions, Interaction networks

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Application should include: CV, application letter, Names and addresses of two references. The application file should be sent before May 14, 2018 to sylvie.ricard-blum@univ-lyon1.fr. The open competitive recruitment process is in two steps: 1. Internal laboratory procedure. 2. Interdisciplinary jury of EDISS.